Universitätsklinik Balgrist
Abteilung für Anästhesiologie
Chefarzt: PD Dr. med. Urs Eichenberger

Betreuung der Masterarbeit: Dr. med. Jose Aguirre
Leitung der Masterarbeit: Prof. Dr. med. Alain Borgeat

The effects of perioperative interventions on postoperative delirium in non-cardiac surgery: A systematic review

MASTERARBEIT

zur Erlangung des akademischen Grades
Master of Medicine (M Med)
der Medizinischen Fakultät der Universität Zürich

vorgelegt von
Pellegrino Alejandro (10-758-142)

2017

Summary

1. Abstract

Background: Postoperative Delirium (POD) is a well-known complication, occurring mainly in elderly patients. The increase in surgical interventions in the elderly population is a challenge for postoperative care units to recognize, treat and prevent this condition. Despite the frequency of this event, there is still space for improvement of management, prophylaxis and treatment. There are a variety of perioperative measures that are currently investigated to possibly reduce the POD incidence and / or to improve its diagnosis and management. To summarize and analyze recent clinical studies in the non-cardiac population, we performed a systematic review.

Objective and Methods: To examine whether there is potential for optimization in modern POD prevention guidelines we reviewed the current literature including prospective clinical trials that assessed perioperative interventions and its effect on the POD incidence.

Results: We found 23 prospective studies including a total of 4'525 patients. The described interventions ranged from simple use of pharmaceutical agents to complex treatment protocols.

Conclusion and Implications: According to the current literature, there is no strong evidence that a specific perioperative measure reduces the POD incidence. However, there are single studies showing a positive effect on the POD incidence with simple measures like geriatric consultation or haloperidol prophylaxis. Especially high-risk patients could profit from these measures.

Additional randomized controlled trial RCTs need to be conducted to verify or refute a positive effect of sedation depth monitoring, various pharmaceutical prophylaxis (Haloperidol, Olanzapine and gabapentin), geriatric care units, fast-track surgery or the use of regional anesthesia techniques.

2. List of abbrevations

BIS: bispectral index
CNS: central nervous system
EEG: electroencephalogram
FICB: fascia iliaca compartment block
FTS: fast track surgery
GABA: gamma-aminobutyric acid
ICU: intensive care unit
i.v.: intravenous
NIRS: near-infrared spectroscopy
POD: post-operative delirium
POCD: post-operative cognitive dysfunction
RCT: randomized controlled trial

3. Introduction

The increasing number of operations performed on elderly patients has raised the question whether anesthesia is harmful for the cerebral function in this patient category. Elderly patients frequently experience postoperatively an acute deterioration of their cerebral functions, resulting in postoperative delirium (POD) or postoperative cognitive dysfunction (POCD). The acute change in the neuropsychiatric state of the patient has a direct influence on the patients' morbidity and mortality. So, to further understand the pathomechanism of anesthesia on the elderly brain, it is important to analyze its physiology and pathophysiology.

3.1 Pathophysiology of age-related neuropsychiatric decline [1]

3.1.1. Brain Volume

Once a brain reaches the age of 45-50, a progressive decline in brain weight begins. As gray matter only increases in childhood and then starts decreasing slowly but continuously, white matter volume usually increases until the age of 45, explaining increases in connectivity between brain regions, and thereafter starts to decrease. This explains the decrease in whole-brain-volume with ageing-associated losses, as age-related comorbidities like diabetes and hypertension can adversely affect changes in white matter tracts [2].

3.1.2. Blood-Brain Barrier

Age has a vast number of effects on the blood-brain barrier such as a decrease in microvascular density and capillary lumen size, as well as a reduction of the number of mitochondria per endothelial cell. These affect the permeability of the blood-brain barrier [3]. Known risk factors for acceleration of these changes include diabetes mellitus, hyperlipidemia, hypertension and adverse drug reactions. The hypothesis that age-associated injury of the blood–brain barrier plays a role in the pathogenesis of white matter disease is vastly supported [3]. Age-related injury in the blood-brain barrier might also modify the reaction to ischemia and the drug permeability into the CNS [3].

3.1.3. Neurogenesis

Physiologically, neural stem cells are constitutively active in the hippocampal dentate gyrus and sub ventricular regions of the lateral ventricles, where they can develop into neurons at every given age [4]. This process called neurogenesis can cause neural plasticity that is involved in cognitive and emotional functions (dentate gyrus). However, neurogenesis decreases gradually with ageing, resulting in a worse ability to learn and contributing to cognitive decline [4].

3.1.4. Inflammation

The CNS can respond to stress by coordinating cytokine-mediated signals within the CNS with the peripheral immune system. The peripheral immune system can cause an inflammatory response of the CNS, which can manifest as behavioral or cognitive changes. The CNS has its own immune cells, namely astrocytes, microglia and CNS-associated macrophages. Microglia are responsible for the response and propagation of signals emitted from the peripheral immune system. The best example is the perioperative period, during which microglia can release cytokines or perform macrophage-like responses. The production of cytokines can be prolonged or exaggerated, if an aged brain has an impaired anti-inflammatory feedback [5]. Increased inflammatory response combined with ageing and systemic diseases (e.g. hypertension) are associated with cognitive changes [6].

3.1.5. Cognition

There are two main ways how cognition changes with age. First, there is acquired knowledge (e.g. vocabulary) that improves up to ~60 years of age, after which it declines. Secondly, you can measure the processing speed (reasoning, memory and spatial cognitive abilities), which decline in a nearly linear fashion from early adulthood [7]. The most dramatic feature that declines with age is memory, as 40% of people aged over 60 suffer from a memory decline, which greatly affects the performance of daily living activities [8].

3.1.6. Cognitive Reserve

Cognitive reserve (passive/active) is defined as the inconsistency between anatomic and functional age-related decline. The brain size or its neuronal count is referred to as passive cognitive reserve, and it is mostly measured by brain volume, synaptic count or dendritic branching. In comparison, active reserve, defined as functional cognitive integrity, is not easy to be measured. There is no 'best measure’; nevertheless, it is usually better in people with higher socioeconomic status and educational attainment. It is known, that post-mortem Alzheimer's disease pathology and pre-mortem cognitive function is modified in people with higher educational attainment; every year of education has a positive effect on the cognitive function for the same neuropathology [9]. A patient's cognitive reserve is a better indicator for their overall cognition, than their underlying neuropathology [9]. Even though it is not known what exactly causes a decrease in functional cognitive reserve, we can observe its manifestation: Decrease in activities of daily living, increased sensitivity to anesthetic agents and increased risk for POD & POCD.

3.1.7. Cerebrovascular Disease

Age-related large vessel arteriosclerotic and small vessel angiopathic cerebrovascular diseases are associated with a few risk factors: Hypertension, diabetes mellitus, elevated plasma homocysteine and apolipoprotein E [10]. These changes in the cerebrovascular system can cause subclinical vascular disease, a condition that is quantified on magnetic resonance images as white matter hyper intensities. Clinical manifestation associated with these lesions include changes in cognition, attention, psychomotor speed and executive functions [11].

3.2 Anesthesia and the elderly brain [1]

Anesthetic agents exert their function on a small number of CNS targets, focusing on postsynaptic ligand-gated ion channels. Some of these agents affect excitatory receptors, whereas others act as potentiators of inhibitory synaptic receptors (e.g. gamma-aminobutyric acid receptors) [12]. Intravenous drugs are known to have an effect on a large variety of receptors: GABA (propofol, etomidate), alpha-2 (dexmetomidine), N-methyl-D-aspartate (ketamine), acetylcholine, adenosine and dopamine (opioids) [13]. However, inhalational anesthetics act on different ion channel receptors, including GABA, glycine, acetylcholine [14], glutamate, and serotonin [15]. The postoperative cognitive problems experienced by the elderly results from the variety and complexity of the interactions between anesthetic drug and ion channels. The CNS cholinergic system is of special importance to neuropsychiatric postoperative decline, as there is a close relationship between cognition and acetylcholine [16]. Therefore, the interaction between anesthetics and acetylcholine receptors may be of crucial importance. As prefrontal cholinergic neurons degenerate with rising age, elderly patients tend to be more susceptible to anesthesia-mediated depression of cholinergic neurotransmission than younger patients [17, 18]. It is therefore important to keep an eye on the anticholinergic medication in surgery patients.

3.3 Monitoring the elderly brain during general anesthesia [1]

Monitoring brain oxygenation/perfusion and depth of anesthesia may be a useful tool for reducing postoperative cognitive decline. An association between cerebral oxygen desaturation and worse cognitive outcomes [19] has been found by intraoperative near-infrared spectroscopy (NIRS). These studies are limited by non-uniform definitions of desaturation and cognitive decline, and inadequate sample-size. Therefore, results of those RCTs were inconclusive. In a similar study, the relevance of impaired age-related autoregulation of cerebral blood flow in elderly patients as a contributory factor to cerebral oxygen desaturation has been discussed but results remain inconclusive as well [20].

Available means of monitoring anesthetic depth are auditory evoked potentials and, more importantly, the electroencephalogram (EEG, processed or raw). The bispectral index (BIS) monitor is the most commonly used EEG in clinical practice. Studies have concluded that improvement in postoperative cognitive outcomes would be possible by having 'lighter' levels of anesthesia [21, 22]. Furthermore, there have been studies reporting no association or even the opposite effect between the monitored anesthesia depth and postoperative cognition [23, 24].

3.4 The elderly patient and sedation [1]

While general anesthesia mainly acts at the level of the brain, regional anesthesia either works in the peripheral nervous system, or near the spinal cord. Common clinical practice suggests sedation, when regional anesthesia is used. Even though this procedure is under-investigated, it is still widely employed in elderly patients, most often for orthopedic procedures. Clinical trials involving younger patients have established dosage and method of administration, even though they did not account for the different pharmacokinetics and pharmacodynamics in elderly patients. However, these results are invariably extrapolated and used on elderly patients, possibly resulting in perioperative cognitive alteration or over dosage [25]. Over dosage could be avoided by using patient-controlled sedation, a method that has been applied in cataract surgery with a high level of patient satisfaction [26], even though it still needs validation for the elderly population and might be only of interest to patients with no pre-morbid cognitive dysfunction.

Sedation monitoring may be a useful tool to prevent over dosage, clinical data suggests. It appears to be more important to always monitor sedation depth, than to choose the right type of sedation monitor. The BIS monitoring, for example, does not correlate with clinical sedation scale scores [27].

3.5 POD – classification & assessment [1]

POCD definition: Acute-onset organic brain syndrome that usually develops within the first couple of postoperative days. Additionally, it must exhibit a fluctuating course and it is usually accompanied by a disturbed circadian rhythm.

3.5.1. Symptoms

Inattention is the main symptom, even though other cognitive changes overlap, for example disorientation or memory deficit. Delirium can be classified as hyperactive, hypoactive or mixed variation depending on the change in psychomotor behavior [28]. Even though the hyperactive form looks more dramatic, the hypoactive form is usually more dangerous and is associated with relatively higher mortality. It is often underdiagnosed as patients exhibit no symptoms on their own

and mostly just lay quietly and motionless. This presentation can be misunderstood as symptoms of dementia and/or depression [29]. POD symptoms usually arise 24-72 h after surgery (the first 24 h are symptomless and therefore called lucid interval) and are distinguished from cognitive 'emergence phenomena' which occur in the transition time from anesthesia to wakefulness [30]. If a patient shows one or more symptoms of delirium, but does not complete all the defined diagnostic criteria, his diagnosis would not be POD but 'subsyndromal delirium' instead [31].

3.5.2. Epidemiology

Depending on the type of surgery, the incidence of POD in elderly patients varies strongly, ranging from an average of 10% to 30-65% in hip fracture, cardiac and emergency surgery [32, 33]. There are specific irreversible risk factors such as advanced age, cognitive impairment, lower educational level and pre-existing medical conditions, as well as potentially reversible risk factors, e.g. malnutrition, electrolyte imbalance, environmental disturbances, substance withdrawal (alcohol or medication), infection and pre-morbid CNS co-medication. In cognitively intact patients, severe pain and inadequate analgesia are individual risk factors for POD [34].

3.5.3. Pathogenesis

While there is still no exact explanation to the pathogenesis of POD, it is generally assumed to be multifactorial. Studies suggest that changes in neurotransmitter levels of acetylcholine, dopamine and melatonin can lead to POD [35]. The high prevalence of POD after a long surgery has been explained by the inflammatory response to the stress of the surgery [36, 37]. An interesting discovery has been the response of microglial cytokines to peripheral immune system stimuli in vitro: cultures exposed to isoflurane, sevoflurane and propofol each have a different cytokine responses [38]. High postoperative pain levels have also been identified as a cause for hyperactive delirium. [39]

3.5.4. Prognosis

As mentioned earlier, suffering from a POD has a negative impact on health prognosis. The longer and more severe POD is associated with higher postoperative mortality [40]. POD per se is associated with short and long-term risk of death, prolonged hospital stay and higher rates of institutionalization following discharge, ultimately increasing total health care expenses [40].

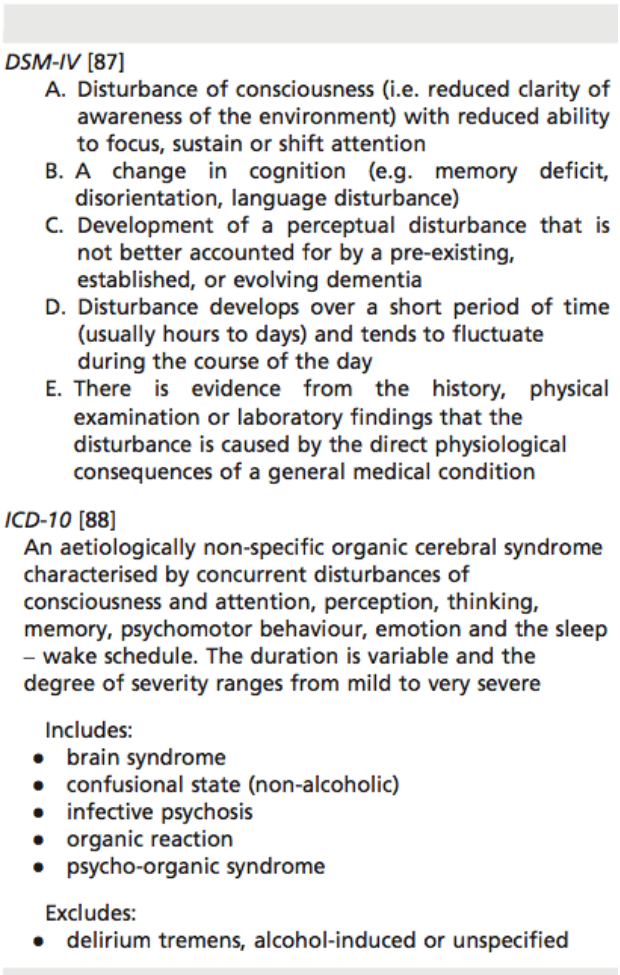
3.5.5. Assessment

The most up to date definition of diagnostic criteria can be found in the International Sta- tistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (Fig. 1). Apart from those

two, there are a number of other diagnostic tools that have been designed and validated to establish the diagnosis of POD. The most important one would be the confusion assessment method (CAM), which is specific, sensitive, reliable and comfortable to use [41]. Delirium is diagnosed as shown in Fig. 2: patients have to present inattention of acute onset with fluctuating course, combined with either disorganized thinking or altered consciousness. This method fails to separate delirium in terms of severity. To assess and diagnose POD in intubated and critically ill patients, a reliable CAM-ICU nonverbal screening tool has been developed [41]. Additionally, the Nursing Delirium screening scale, the Delirium Detection Score [42] and the Intensive Care Delirium Screening checklist (ICDSC) [43] are acceptable means to screen for delirium.

Fig. 1: Diagnostic criteria according to DSM-IV and ICD-10.

Fig. 2: POD assessment according to CAM.



DSM-IV [87]

A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention
B. A change in cognition (e.g. memory deficit, disorientation, language disturbance)
C. Development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia
D. Disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
E. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

ICD-10 [88]

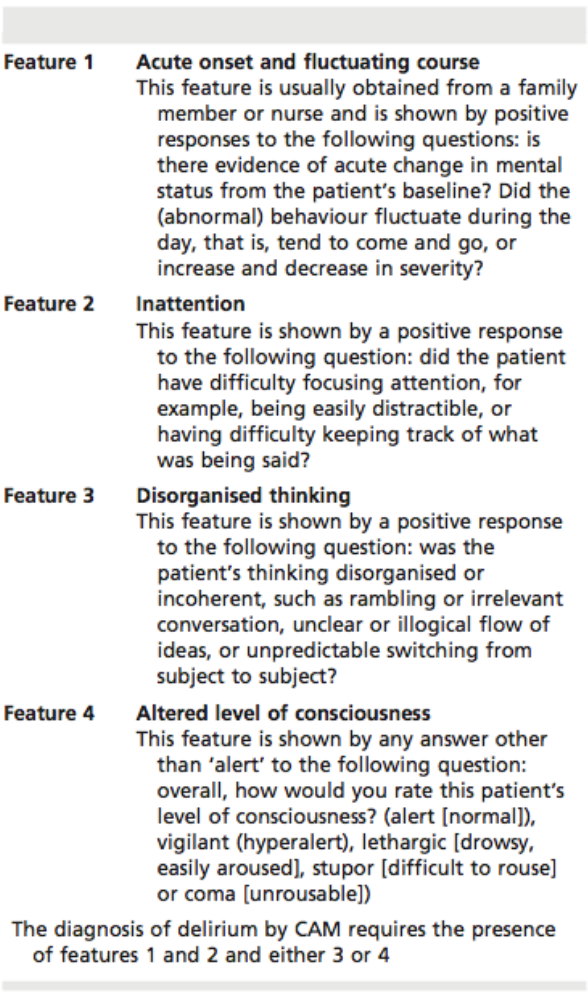
An aetiologically non-specific organic cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep – wake schedule. The duration is variable and the degree of severity ranges from mild to very severe

Includes:

- brain syndrome
- confusional state (non-alcoholic)
- infective psychosis
- organic reaction
- psycho-organic syndrome

Excludes:

- delirium tremens, alcohol-induced or unspecified



Feature 1 **Acute onset and fluctuating course**
This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: is there evidence of acute change in mental status from the patient's baseline? Did the (abnormal) behaviour fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

Feature 2 **Inattention**
This feature is shown by a positive response to the following question: did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

Feature 3 **Disorganised thinking**
This feature is shown by a positive response to the following question: was the patient's thinking disorganised or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4 **Altered level of consciousness**
This feature is shown by any answer other than 'alert' to the following question: overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant (hyperalert), lethargic [drowsy, easily aroused], stupor [difficult to rouse] or coma [unrousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4

3.6 POD - Treatment and prevention [44]

Emergency pharmacologic treatment is mostly not indicated. It would be needed in case of dangerous agitation associated with hyperactive delirium [45]. At first, it is important to exclude organic issues and consider alternative treatment strategies. Haloperidol, a neuroleptic (antipsychotic) agent should be considered for sedation, as it does not depress respiration [46]. However, haloperidol prophylaxis has different effects on delirium outcome, which will be discussed later. There is evidence that the use of delirium assessment scores in ICU setting can reduce haloperidol dosage and treatment duration [47]. Alternative measures would include treatment of sleep disorders, immobility, dehydration, visual and hearing impairment and cognitive dysfunction. These measures reduce the incidence of delirium in hospitalized elderly patients [48]. In ICU patients, rehabilitation strategies consisting of interruption of sedation, physical and occupational therapy in the early days of illness, have been shown to reduce duration of delirium [49].

Knowing that the biochemistry of the brain and the hormone regulation are strongly affected by medication, Clegg et al. reported a list of medicaments that should be avoided in patients at risk for POD: opioids, benzodiazepines, dihydropyridines and histamine H1-receptor agonist [50].

There is no clinical guideline for prophylactic pharmacological therapy. However, it seems, that pain management is of utter importance. In mechanically ventilated ICU patients there is some evidence suggesting dexmedetomidine (2-adrenoreceptor) as a prophylactic medicament. According to Duggleby, this measure would increase the number of delirium-free days [51]. Dexmedetomidine shows clear superiority over benzodiazepines, as it has an analgesic effect, does not cause respiratory depression and results in a different sedation, which enables the patient to be more interactive and communicative [52]. In comparison with lorazepam and midazolam, dexmedetomidine resulted in shorter duration of mechanical ventilation and a reduced incidence of delirium, with no effect on ICU or hospital stay [52 53].

The strongest factor associated with POD would be cognitive impairment, as delirium and dementia are closely related [54]. Approximately 50% of patients suffering from delirium will develop dementia [55]. In addition, preoperative depression is a negative predictive factor, as it increases significantly the risk for POD [56].

Considering predisposing factors for POD is nearly impossible, nevertheless, a validated model has been developed for delirium prediction. It is based on four criteria evaluated using specific scales: Illness severity (Acute Physiology and Chronic Health Evaluation Score) [57], visual impairment (Schnellen Test) [58], cognitive impairment (Mini Mental State Evaluation Score) [59] and serum urea/creatinine ratio [60]. Following this model, Kalisvaart reported an incidence of

POD of 37% in high-risk hip fracture surgery patients, compared to 3.8% in the low-risk group [61].

4. Objectives

Due to the confounding results in the literature with different approaches to prevent POD, using or not adequate POD diagnostic tools for clinical studies, we performed this qualitative systematic review. The aim of this review was to determine the efficacy of pharmacological and non-pharmacological peri-operative interventions to decrease delirium

Our research question was: "Which peri-operative interventions during non-cardiac surgery have been associated with a reduction in delirium within the first seven postoperative days?'

4.1. Why a qualitative systematic review?

According to evidence based medicine (EBM), systematic reviews and meta-analyses of good quality studies can be the best form of evidence available for clinicians. EBM combines the best available research evidence along with clinical experience and patient needs and expectations [62].

This concept begun with Gordon Guyatt and his group at McMaster University in 1992 [63].

Since 1998 more than 1000 publications addressed the topic. Different factors contributed to the increased importance of EBM:

- physicians daily need relevant information of best quality regarding diagnosis, treatment, and prognosis,
- the traditional information sources are frequently old, not updated, or of excessive volume,
- the divergence in improved clinical experience from decreased scientific study knowledge over time; and
- time constraints with often only a few minutes per week for reading and review.

Recent developments have helped to overcome these barriers such as:

- new strategies for tracking and evaluating evidence,
- journals focused on evidence-based medicine,
- technological improvement for faster literature search; and
- systematic reviews of healthcare studies [62].

In earlier times, expert opinion has been presented in narrative reviews which are not evidence-based, and, consequently have limitations [64-65].

Unsystematic narrative reviews often include only research selected by the authors, increasing the risk of selection bias [66-67] Cook et al defined a systematic review as "the application of scientific

strategies that limit bias by the systematic assembly, critical appraisal and synthesis of all relevant studies on a specific topic." [68].

Therefore, systematic reviews are work intensive and require expertise in the subject, the literature and the review methods.

Appropriate questions to be addressed in a systematic review are:

- disease or condition frequency,
- phenomena associated with disease or interventions,
- diagnostic accuracy,
- disease etiology and / or risk factors,
- prognosis; and
- intervention effects [69]

Also, the aims of the systematic review have to be clarified. They can include:

- summarizing an overwhelming amount of literature,
- resolving literature conflicts,
- clarifying the relative strengths and weaknesses of the literature on the specific question,
- avoiding further redundant trials,
- evaluating the need for a large clinical trial,
- improving the statistical power of smaller studies,
- enhancing the precision and / or identify a smaller treatment effect; and
- improving the generalizability of treatment outcomes [70].

When studies have sufficiently similarities, a meta-analysis, with statistical pooling of data from individual studies, might be appropriate. When the results of several studies are apparently similar, a meta-analysis can lead to a more precise (narrower confidence intervals) overall estimate of the treatment effect. However, using very narrow inclusion criteria to create more homogenous data, lead to exclusion of patients with special characteristics, resulting in less generalizable data. Therefore, it can be very inappropriate to pool dissimilar studies in a meta-analysis, but it is for sure never inappropriate to undertake a qualitative systematic review. If studies are dissimilar, a descriptive summary of the studies in a qualitative systematic review should be performed. However, reviewers often narrow inclusion criteria to possibly avoid heterogeneity by including only studies

reporting a particular outcome, or by limiting the review to specific study designs [71] The drawback of this approach is it biases the review against potentially valuable studies not reporting an outcome in the requested manner [72]. Often, the studies meeting certain inclusion criteria may represent heterogeneous studies which should not be combined for statistical evaluation [73]. Therefore, a qualitative systematic review of available data following clearly defined methods allows clinicians a certain space in evaluating the best evidence.

Systematic reviews and meta-analyses of Level 1 and 2 studies represent the highest level of evidence.

5. Methods

5.1. Qualitative systematic review configuration

To avoid different bias the review configuration was performed according to the advises of different experts [70, 74] and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [75] and the Cochrane Handbook for Systematic Reviews of Interventions [76].

The following steps were performed to achieve a good qualitative systematic review:

- Formulation of a clear research question
- Literature Search
- Data Extraction
- Quality Appraisal
- Data Analysis and Results
- Interpretation of Results

5.2. Literature search

A computerized search of the electronic databases PubMed, EMBASE and the Cochrane Controlled Trials Register for papers published between January 1990 and January 2016 was performed. Only studies in the English language and performed on adults were considered. Maximally expanded search terms with Boolean operators for the terms (delirium).mp; (cognitive disorder).mp; and (surgery).mp. Exclusions were (cardiac surgery or coronary artery bypass or CABG).mp. Moreover, the clinical trials database, ClincalTrials.gov, was searched. An additional manual search for theme-related review articles and other relevant material was performed to identify other studies in a snowballing technique. A manual search of the reference lists of all included papers was also conducted for further eligible studies. All reviews, retrospective studies, letters, case reports, comment, editorials and guidelines were removed, as were duplicate publications. Duplicates were eliminated

5.3. Eligibility criteria

Eligible trials had to diagnose delirium using a test recommended by the Diagnostic and Statistical Manual of Mental Disorders (DSM): DSM-III; DSM-III-R; DSM IV [77]

or by the International Classification of Diseases, 10th edition [78].

We included only prospective studies like randomized controlled trials (RCTs) or cohort studies comparing two groups (intervention and no intervention) with assessment of delirium in the first 7 postoperative days. Studies which used pre-operative and postoperative mini-mental state examinations (MMSE) in the diagnosis of delirium were excluded. Case series without controls as well as retracted publications were excluded from the analysis.

5.4. Data extraction

Two reviewers independently assessed each title for inclusion (A.P., J.A.A.), and relevant abstracts were independently evaluated. If doubt existed regarding relevance, the full text article was assessed. Both reviewers independently extracted in duplicate relevant information. Any conflicts were resolved by a third independent reviewer (A.B.). The relevant information extracted is presented in Table 1.

This systematic review was performed in accordance with the PRISMA guidelines [79].

5.5. Risk of bias

To avoid inclusion, bias all study designs allowing a good quality review (RCTs and cohort studies) were included without excluding any due to a quality score pre-screening.

Two independent reviewers (C.O. and J.A.A.) performed the screening and assessed each title for inclusion, and relevant abstracts were independently evaluated. In the case of any doubt, the full text article was assessed. A third reviewer (A.B) was available to resolve possible conflicts.

Two reviewers (A.P. and J.A.A.) independently extracted in duplicate relevant information. Possible conflicts were resolved by the third independent reviewer (A.B.).

6. Results

6.1. Study selection

We identified 1376 studies from our literature search, of which 39 studies were selected for full paper analysis. From these studies, 23 finally met the eligibility criteria and were included in the review. The seventeen excluded studies were extensively assessed but excluded because of a different primary outcome or insufficient assessment for POD. (Table 6)

6.2. Study characteristics and risk of heterogeneity

The detailed characteristics of the included studies are shown in tables 1&2. Even though most of the studies are randomized, prospective trials, a great heterogenicity among them was noted. Six different assessment methods where used. We found many valuable studies with insufficient assessment tools such as the mini-mental state examinations, which we could not include in this review. Used in 12 studies, the CAM protocol was the most common method. Also, the time points for reading out where very heterogenous. Additionally, the studies vary in population size ranging from 11 to 1'028 patients. Moreover, the type of surgery varies widely with orthopedic procedures being the most frequently assessed ones (12 out of 23).

6.3. Risk of bias across the studies

To avoid inclusion, bias all study designs allowing a good quality review (RCTs, cohort studies, case control studies and case series with control groups) were included [74]. Compared to other reviews [80] we did not accept MMSE as diagnostic tool for postoperative delirium. Additionally, compared to another review [81] we did not include studies which were interrupted due to randomization and other methodological problems.

6.4. Results in individual studies

Table 2 presents a summary of the setup protocols as well as the main results from each study, helping to compare the findings. Overall nine RCTs [82-84, 88-91, 100, 104] and one randomized, comparative clinical study [86] showed a significant impact on our primary outcome (delirium incidence) towards the study group. On the other hand, we have 10 RCTs [85, 87, 90, 93-96, 99, 101, 103] and 3 randomized trials [97, 98, 102] that show no significant difference between the groups.

In tables 3 – 5 the different interventions showing an impact and showing no impact on postoperative delirium are summarized. Four different pharmaceutical interventions showed a positive effect: haloperidol [82, 100], diazepam/flunitrazepam [84], gabapentin [90], and olanzapine [94]. However, in two other studies [86, 103] haloperidol was shown not to be effective in preventing

postoperative delirium. Other medication like donepezil [87, 92, 98] and melatonin [102] showed no effect in preventing postoperative delirium. From the perioperative anesthetic interventions, the fascia iliaca compartment block for hip surgery [93] and a light sedation [95] compared to a deep sedation was shown to be effective. The use of propofol compared to sevoflurane [85], regional to general [88, 97] as well as the intraoperative use of N2O compared to O2 [89] had no impact on the incidence of POD. Additional positive perioperative measures were geriatric consultation with a specific set up for elderly patients showed to be effective [83, 99] as was the use of fast track surgery [104]. The use of light therapy [91, 96] and a different specific geriatric setup [101] did not show any effect on the incidence of postoperative delirium.

Table 1. Study characteristics

Study	Design	No. of patients	Surgery	Read Out	Time Points of Read Out
Kaneko et al. (1999) [82].	randomized, comparative clinical study	78	GIT-surgery	DSM-III-R	On the 5th post-op day, information was gathered and evaluated
Marcantonio et al. (2001) [83].	RCT	177	orthopaedic	CAM	Daily
Aizawa et al. (2002) [84].	RCT	42	laparotomy	DSM IV	2x/d for 7 days after surgery
Nishikawa et al (2004) [85].	Randomized clinical trial	50	laparoscopy	DRS	Three times daily until 3rd post-op day
Kalisvaart et al. (2005) [86].	RCT	430	orthopaedic	DSM IV, CAM, DRS	Daily
Liptzin et al. (2005) [87].	RCT	1038	orthopaedic	DSM IV, CAM	Daily
Papaioannou et al. (2005) [88].	Randomized study	47	elective surgery	DSM-III	Daily until 3rd post-op day
Leung et al. (2006) [89].	RCT	114	non-cardiac surgery	CAM	24 & 48h after surgery.
Leung et al. (2006) [90].	RCT	21	Spinal surgery	CAM	not really mentioned, I suppose according to the CAM protocol
Taguchi et al. (2007) [91].	RCT	11	Oesophagal cancer surgery	NEE-CHAM	Twice daily until 5th post-op day.
Samson et al. (2007) [92].	RCT	33	orthopaedic	DSM-IV	Three times daily until 4th post-op day
Mouzopulus et al. (2009) [93].	RCT	219	orthopaedic	DSM IV & CAM	Daily
Larsen et al. (2010) [94].	RCT	495	orthopaedic	DSM-III-R, CAM	Daily until 8th post-op day or discharge
Sieber et al. (2010) [95].	RCT	114	orthopaedic	CAM	From the second post-op day until discharge daily
Ono et al. (2011) [96].	RCT	22	Oesophagectomy	NEE-CHAM & DSM-IV TR	Twice daily until 6th post-op day
Slor et al. (2011) [97].	RCT	527	orthopaedic	DSM-IV & CAM	Daily until discharge
Marcantonio et al. (2011) [98].	RCT	16	orthopaedic	CAM	Daily until discharge and after 2, 4, 6 weeks for follow-up

Table 1 ff. Study characteristics

Study	Design	No. of patients	Surgery	Read Out	Time Points of Read Out
Deschodt et al. (2012) [99].	RCT	171	orthopaedic	CAM	According to CAM (1,3,5,8,15 days post-op)
Wang et al. (2012) [100].	RCT	457	non-cardiac surgery	CAM	1x/d until 7th post-op day
Hempenius et al. (2013) [101].	RCT	260	tumour-surgery	DOS, DSM-IV, DRS-R-98	Three times daily until discharge
De Jonghe et al. (2014) [102].	RCT	378	orthopaedic	DSM-IV	Daily until 8th post-op day or discharge
Fukata et al. (2014) [103].	randomized, open-label prospective trial	119	GIT-surgery, orthopaedic	NEE-CHAM	Daily until 7th post-op day
Jia et al. (2014) [104].	RCT	233	GIT-surgery	DRS-R-98	On admissdion, then daily until 5th post-op day

Table 2. Study setups and main results

Study	**Special Setup**	**Results**
Kaneko et al. (1999) [82].	78 patients who underwent gastrointestinal surgery received either 5 mg of haloperidol intravenously postoperatively at 21:00 for 5 consecutive days, or normal saline with the same schedule.	There was a significant decrease in delirium incidence in the haloperidol group.
Marcantonio et al. (2001) [83].	The subjects randomized to the intervention group underwent geriatric consultation preoperatively or within 24 hours postoperatively. A geriatrician performed daily visits and made targeted recommendations based on a structured protocol.	There was a statistically significant reduction of delirium incidence in the geriatrician care group compared with the usual care group.
Aizawa et al. (2002) [84].	Delirium-free protocol (DFP): Diazepam (0.1 mg/kg) i.m. 20:00, Flunitrazepam (0.04 mg/ kg) i.v + Pethidin (1 mg/KG) i.v 20:00 for 8 hours	There was a significant decrease in delirium incidence in the DFP group.
Nishikawa et al (2004) [85].	The patients were randomly assigned by a sealed envelope technique to a propofol group or a sevoflurane group.	There was no significant difference between the incidences of delirium in the two groups during the first 3 days after surgery.
Kalisvaart et al. (2005) [86].	Eligible patients were sequentially randomly assigned to study treatment (placebo or haloperidol 0.5 mg three times daily) from a block of drugs that the hospital pharmacist had prepackaged.	There was no significant difference between the incidences of delirium in the two groups.
Liptzin et al. (2005) [87].	Patients were randomized separately by a research pharmacist to 5 mg of donepezil or placebo with breakfast. Subjects were given the study medication and told to begin taking it 14 days before the surgery and to continue it for 14 days after the surgery.	There was no significant difference between the incidences of delirium in the two groups.
Papaioannou et al. (2005) [88].	Patients were randomly assigned by a computer program to receive either general or regional anaesthesia (epidural or spinal) with or without conscious sedation by propofol infusion to achieve a Ramsay sedation score of 2.	There was no significant difference between the incidences of delirium in the two groups.
Leung et al. (2006) [89].	The intraoperative anaesthetic management was randomized to either N_2O with O_2, or O_2 (with or without air) plus a potent inhalational agent for both groups	There was no significant difference between the incidences of delirium in the two groups.
Leung et al. (2006) [90].	Either gabapentin 900 mg or placebo was administered by mouth 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days.	The incidence of postoperative delirium was higher in the placebo than in the gabapentin groups.

Table 2 ff. Study setups and main results

Study	**Special Setup**	**Results**
Taguchi et al. (2007) [91].	Bright light therapy was started on the day after extubation. The subjects were exposed to light for 2 h from 7:30 h to 9:30 h in the morning from days 2 to 5 after surgery, in principle, with modifications according to the condition of each patient.	There was no significant difference between the incidences of delirium in the two groups.
Samson et al. (2007) [92].	Subjects received their first dose of study medication post-operatively, therefore subjects took 5 mg of donepezil or placebo every 24 h from this time point (3 h) for three days. Thus the total duration of treatment was 4 days.	There was no significant difference between the incidences of delirium in the two groups.
Mouzopulus et al. (2009) [93].	FICB was administered with a 0.25 mg dose of 0.3 mL/kg bupivacaine on admission and repeated daily every 24 h until delirium occurrence or hip surgery was performed. Twenty-four hours after hip surgery the same dose of FICB was re-administered and repeated daily every 24 h until delirium occurrence or discharge.	The incidence of delirium in the FICB prophylaxis group was significantly lower from the incidence in the placebo group.
Larsen et al. (2010) [94].	Olanzapine 5 mg or placebo were given immediately before and after surgery.	The incidence of postoperative delirium was lower in the olanzapine group than in the placebo group for the entire sample.
Sieber et al. (2010) [95].	Sedation depth was titrated using processed electroencephalography with the bispectral index (BIS), and patients were randomized to receive either deep (BIS, approximately 50) or light (BIS, ≥80) sedation.	The prevalence of postoperative delirium was significantly lower in the light sedation group, indicating that 1 incident of delirium will be prevented for every 4.7 patients treated with light sedation
Ono et al. (2011) [96].	Beginning at Day 2, participants in the study group underwent two hours of bright light exposure starting at 7:30 a.m. for a total of four days.	There was no significant difference between the incidences of delirium in the two groups.
Slor et al. (2011) [97].	Postoperative delirium was compared between groups receiving general and regional anesthesia and between groups with and without specific perioperatively administered drugs grouped according to class.	There was no significant difference between the incidences of delirium in the two groups.

Table 2 ff. Study setups and main results

Study	**Special Setup**	**Results**
Marcantonio et al. (2011) [98].	The research pharmacy placed donepezil 5 mg tablets into capsules, and prepared matching capsules filled with placebo. The study drug was administered daily, unless adverse events supervened, for a total treatment course of 30 days	There was no significant difference between the incidences of delirium in the two groups.
Deschodt et al. (2012) [99].	geriatric consultation: geriatrician nurse, social worker, occupational therapist + physiotherapy, preoperative assessment	Significantly more controls than intervention group participants were delirious at any point after surgery.
Wang et al. (2012) [100].	Study drug was administrated by bolus injection of 5 mL (0.5 mg haloperidol or placebo), followed by continuous infusion at a rate of 1 mL/hr for 12 hours (0.1 mg/hr haloperidol or placebo).	There was a significant decrease in delirium incidence in the haloperidol group.
Hempenius et al. (2013) [101].	Patients in the intervention group were assessed preoperatively by a geriatric team and monitored during their hospital stay. An individual treatment plan was drawn up paying specific attention to patient-related risk factors for delirium, namely, cognitive impairment, visual impairment, hearing impairment, malnutrition and impaired mobility. During their hospital stay, the patients in the intervention group were assessed daily by a geriatric nurse.	There was no significant difference between the incidences of delirium in the two groups.
De Jonghe et al. (2014) [102].	Patients received melatonin 3 mg or placebo in the evening for 5 consecutive days, starting within 24 hours after admission.	There was no significant difference between the incidences of delirium in the two groups.
Fukata et al. (2014) [103].	Haloperidol 0.5A (2.5 mg) was dissolved in 100 ml of saline and intravenously administered by drip infusion once daily at 18:00 from postoperative days 1 to 3 to the intervention group. The non-intervention group did not receive preventive treatment.	There was no significant difference between the incidences of delirium in the two groups.
Jia et al. (2014) [104].	Patients were randomly assigned into the traditional therapy group (n =120) and the FTS group (n =120).	The incidence of postoperative delirium was significantly lower in patients with the fast track therapy than with the traditional therapy.

Table 3: Perioperative pharmaceutical interventions

Positive Effect on Primary Outcome	No Effect on Primary Outcome
Kaneko et al. (1999) [82]: 78 patients who underwent gastrointestinal surgery received either 5 mg of haloperidol intravenously postoperatively at 21:00 for 5 consecutive days, or normal saline with the same schedule.	Kalisvaart et al. (2005) [86]: Eligible patients were sequentially randomly assigned to study treatment (placebo or haloperidol 0.5 mg three times daily) from a block of drugs that the hospital pharmacist had prepackaged.
Aizawa et al. (2002) [84]: Delirium-free protocol (DFP): Diazepam (0.1 mg/ kg) i.m. 20:00, Flunitrazepam (0.04 mg/ kg) i.v + Pethidin (1 mg/ kg) i.v 20:00 for 8 hours	Liptzin et al. (2005) [87]: Patients were randomized separately by a research pharmacist to 5 mg of donepezil or placebo with breakfast. Subjects were given the study medication and told to begin taking it 14 days before the surgery and to continue it for 14 days after the surgery.
Leung et al. (2006) [90]: Either gabapentin 900 mg or placebo was administered by mouth 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days.	Samson et al. (2007) [92]. Subjects received their first dose of study medication post-operatively, therefore subjects took 5 mg of donepezil or placebo every 24 h from this time point (3 h) for three days. Thus, the total duration of treatment was 4 days.
Larsen et al. (2010) [94]: Olanzapine 5 mg or placebo were given immediately before and after surgery.	Marcantonio et al. (2011) [98]: The research pharmacy placed donepezil 5 mg tablets into capsules, and prepared matching capsules filled with placebo. The study drug was administered daily, unless adverse events supervened, for a total treatment course of 30 days
Wang et al. (2012) [100]: Study drug was administrated by bolus injection of 5 mL (0.5 mg haloperidol or placebo), followed by continuous infusion at a rate of 1 mL/hr for 12 hours (0.1 mg/hr haloperidol or placebo).	De Jonghe et al. (2014) [102]. Patients received melatonin 3 mg or placebo in the evening for 5 consecutive days, starting within 24 hours after admission.
	Fukata et al. (2014) [103]: Haloperidol 0.5A (2.5 mg) was dissolved in 100 ml of saline and intravenously administered by drip infusion once daily at 18:00 from postoperative days 1 to 3 to the intervention group. The non-intervention group did not receive preventive treatment.

Table 4: Perioperative anesthetic interventions

Positive Effect on Primary Outcome	No Effect on Primary Outcome
Mouzopulus et al. (2009) [93]: FICB was administered with a 0.25 mg dose of 0.3 mL/kg bupivacaine on admission and repeated daily every 24 h until delirium occurrence or hip surgery was performed. Twenty-four hours after hip surgery the same dose of FICB was re-administered and repeated daily every 24 h until delirium occurrence or discharge.	Nishikawa et al (2004) [86]: The patients were randomly assigned by a sealed envelope technique to a propofol group or a sevoflurane group.
Sieber et al. (2010) [95]: Sedation depth was titrated using processed electroencephalography with the bispectral index (BIS), and patients were randomized to receive either deep (BIS, approximately 50) or light (BIS, ≥80) sedation.	Papaioannou et al. (2005) [88]. Patients were randomly assigned by a computer program to receive either general or regional anesthesia (epidural or spinal) with or without conscious sedation by propofol infusion to achieve a Ramsay sedation score of 2.
	Leung et al. (2006) [89]: The intraoperative anesthetic management was randomized to either N2O with O2, or O2 (with or without air) plus a potent inhalational agent for both groups
	Slor et al. (2011) [97]: Postoperative delirium was compared between groups receiving general and regional anesthesia and between groups with and without specific perioperatively administered drugs grouped according to class.

Table 5: Other Perioperative Interventions

Positive Effect on Primary Outcome	No Effect on Primary Outcome
Marcantonio et al. (2001) [83]: The subjects randomized to the intervention group underwent geriatric consultation preoperatively or within 24 hours postoperatively. A geriatrician performed daily visits and made targeted recommendations based on a structured protocol.	Taguchi et al. (2007) [91]: Bright light therapy was started on the day after extubation. The subjects were exposed to light for 2 h from 7:30 h to 9:30 h in the morning from days 2 to 5 after surgery, in principle, with modifications according to the condition of each patient.
Deschodt et al. (2012) [99]: geriatric consultation: geriatrician nurse, social worker, occupational therapist + physiotherapy, preoperative assessment	Ono et al. (2011) [96]: Beginning at Day 2, participants in the study group underwent two hours of bright light exposure starting at 7:30 a.m. for a total of four days.
Jia et al. (2014) [104]: Patients were randomly assigned into the traditional therapy group (n =120) and the FTS group (n =120).	Hempenius et al. (2013) [101]: Patients in the intervention group were assessed preoperatively by a geriatric team and monitored during their hospital stay. An individual treatment plan was drawn up paying specific attention to patient-related risk factors for delirium, namely, cognitive impairment, visual impairment, hearing impairment, malnutrition and impaired mobility. During their hospital stay, the patients in the intervention group were assessed daily by a geriatric nurse.

Table 6: Excluded studies

Study	Reason for exclusion
Beaussier et al. (2006)	Primary Outcome is not delir, but the length of hospital stay.
Akarsu et al. (2012)	Assessment of POD was not sufficient (MMSE)
Coi et al. (2012)	Assessment of POD was not sufficient (MMSE)
Jildenstal et al. (2011)	Assessment of POD was not sufficient (MMSE)
Chen et al. (2001)	Assessment of POD was not sufficient (MMSE)
Chan et al. (2013)	Primary Outcome is not delir, but POCD incidence after 3 Months
Lundstrom et al. (2007)	Primary Outcome is not delir, but number of days of postoperative delirium
Berggren et al. (1987)	Primary Outcome is not delir, but postoperative confusion
Kudoh et al. (2002)	Primary outcome is not delir but deteriation of depressive symptoms.
Gruber-Baldini et al. (2013)	Primary outcome is severity of POD.
Williams-Russo et al. (1995)	Primary Outcome is change in cognitive function
Nishikawa et al. (2007)	Primary outcome is not delir, but the quality of postoperative analgesia.
Kudoh et al. (2004)	Primary outcome is not delir, but "Quality of anesthesia recovery such as nausea, vomiting, headache, pain
Mann et al. (2000)	Primary outcome is not delir, but pain relief.
Lurati et al. (2012)	Primary outcome is myokardial ischemia and not delir.
Williams-Russo et al. (1999)	Primary outcome is cognitive dysfunction and not delir.
Musclow et al. (2012)	Primary outcome is not delir, but the quality of postoperative analgesia.

7. Discussion

7.1. Main findings

This review aims to analyze, summarize, and compare recent literature regarding perioperative measures to reduce incidence of POD in non-cardiac surgery. Twenty-three studies were analyzed (19 RCTs, 4 randomized clinical studies). (Tables 1&2) Given the great range of outcomes and measures analyzed, as well as the heterogenicity of the studies characteristics, the findings were inconclusive and interpretations prove to be difficult. Overall, the current findings are not sufficiently robust to indicate clear guidelines for POD prophylaxis.

7.2. Results in context

According to our finding, perioperative geriatric consultations, which included multicomponent interventions, lighter as opposed to deeper anesthesia and the use of haloperidol seems to be effective in decreasing postoperative delirium. (Tables 3-5)

Considering the depth of anesthesia, Sieber et al. found that light sedation (BIS > 80) during spinal anesthesia for orthopedic surgery decreased the occurrence of delirium by 50% when compared with deep sedation (BIS ~50) ($p = 0.02$) [95].

For perioperative geriatric consultation, the clinical trials are at a high risk of bias due to inadequate randomization and/or blinding. (Table 5) Also, the set up deep vs light anesthesia showed significant heterogeneity, and there may be publication bias associated with this intervention. These findings go in accordance with the review by Moyce Z. et al. [80]. Surprisingly, there seems to be no difference in the use of regional vs general anesthesia. (Table 4) This goes in accordance with a meta-analysis of the efficacy of general and regional anesthesia, which failed to show a significant difference (five studies) concerning postoperative delirium, but found that general anesthesia may increase the risk of developing postoperative cognitive dysfunction compared to regional anesthesia [81].

We found a trend to protection with the use of haloperidol. (Table 3) However, the dose of haloperidol varied between the studies. Wang et al. [100] used 0.5 mg haloperidol as an intravenous bolus postoperatively, followed by an infusion at 0.1 mg/h for 12 h; Kaneko et al. [82] administered 5 mg haloperidol i.v. daily for five days, and Kalisvaart et al. [86] used oral haloperidol 1.5 mg pre-operatively and continued for three days postoperatively.

A recent meta-analysis by Teslyar P et al. [105] studied the antipsychotics as a group (haloperidol, olanzapine and risperidone) and also described a trend to a reduction in delirium with the perioperative use of antipsychotics.

Leung et al. [90] found that postoperative use of gabapentin decreased the incidence of delirium, which was probably due to a secondary opioid sparing effect.

7.3. Strengths and limitations

There are some limitations to this review. First, according to other meta-analysis dealing with delirium and postoperative cognitive dysfunction, most of the studies also included in this review seem to be under-powered [80]. Only further research with adequately powered studies will finally show if interventions like geriatric consultation or light sedation are efficient. Second, most of the studies were limited to orthopedic surgery. Delirium research needs to be extended to other non-cardiac surgeries. Additionally, the nature of multi-component consultations includes the bias due to poor randomization and blinding. In the pharmacological intervention studies, there was no standardization of the anesthetic and pharmacological intervention techniques. We also excluded foreign language studies, which could have impacted the results of this review. Finally, only few studies assessed the pre-operative risks for delirium, and there was a lack of standardization considering the timing of postoperative testing.

7.4. Implications for practice

The main findings of this review are that peri-operative geriatric consultations involving multi-component interventions, and lighter anesthesia, seem to be potentially effective in decreasing the outcome of delirium. The use of haloperidol is controversial but potentially beneficial.

7.5. Implications for research

The multifactorial nature of delirium possibly asks for a multiple intervention modality as shown in this review. The approach as peri-operative geriatric consultations have been shown to be powerful interventions to decrease delirium. The peri-operative geriatric consultation is a proactive, comprehensive geriatric assessment along with management and rehabilitation to decrease the outcome of delirium. This modality in combination with the use of antipsychotics and light sedation should be further studied in the elderly population.

Moreover, despite regional anesthesia does not directly interfere with the brain function, good data are missing to correctly assess the possible advantages of these techniques.

A standardized protocol for pre-operative risk assessment and outcome determination is also needed in future studies.

8. References

1. Strøm, C, Rasmussen L.S. and Sieber F.E.: Should general anaesthesia be avoided in the elderly? Anaesthesia 2014; 69 Suppl 1 : 35-44.
2. Aine CJ, Sanfratello L, Adair JC, Knoefel JE, Caprihan A, Ste- phen JM. Development and decline of memory functions in normal, pathological and healthy successful aging. Brain Topography 2011; 24: 323–39.
3. Zeevi N, Pachter J, McCullough LD, Wolfson L, Kuchel GA. The blood-brain barrier: geriatric relevance of a critical brain-body interface. Journal of the American Geriatrics Society 2010; 58: 1749–57.
4. Couillard-Despres S, Iglseder B, Aigner L. Neurogenesis, cellular plasticity and cognition: the impact of stem cells in the adult and aging brain – a mini-review. Gerontology 2011; 57: 559–64.
5. Corona AW, Fenn AM, Godbout JP. Cognitive and behavioral consequences of impaired immunoregulation in aging. Journal of Neuroimmune Pharmacology 2012; 7: 7–23.
6. Ownby RL. Neuroinflammation and cognitive aging. Current Psychiatry Reports 2010; 12: 39–45.
7. Salthouse TA. Neuroanatomical substrates of age-related cognitive decline. Psychological Bulletin 2011; 137: 753–84.
8. Small S. Age-related memory decline: current concepts and future directions. Archives of Neurology 2001; 58: 360–4.
9. Stern Y. Cognitive reserve. Neuropsychologia 2009; 47: 2015– 28.
10. Grindberg LT, Thal DR. Vascular pathology in the aged human brain. Neuropathology 2010; 119: 277–90.
11. Warsch JR, Wright CB. The aging mind: vascular health in normal cognitive aging. Journal of the American Geriatrics Society 2010; 58: S319–24.
12. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. Nature 1994; 367: 607–14.
13. Brown EN, Purdon PL, Van Dort CJ. General anaesthesia and altered states of arousal: a systems neuroscience analysis. Annual Review of Neuroscience 2011; 34: 601–28.
14. Rossman AC. The physiology of the nicotinic acetylcholine receptor and its importance in the administration of anaesthesia. American Association of Nurse Anesthetists Journal 2011; 79: 433–40.
15. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. New England Journal of Medicine 2003; 348: 2110–24.

16. Pratico C, Quattrone D, Lucanto T, et al. Drugs of anaesthesia acting on central cholinergic system may cause post-operative cognitive dysfunction and delirium. Medical Hypotheses 2005; 65: 972–82.
17. Fodale V, Quattrone D, Trecroci C, Caminiti V, Santamaria LB. Alzheimer's disease and anaesthesia: implications for the central cholinergic system. British Journal of Anaesthesia 2006; 97: 445–52.
18. Jansson A, Olin K, Yoshitake T, et al. Effects of isoflurane on prefrontal acetylcholine release and hypothalamic response in young adult and aged rats. Experimental Neurology 2004; 190: 535–43.
19. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. Anesthesia and Analgesia 2013; 116: 663–76.
20. Burkhart CS, Rossi A, Dell-Kuster S, et al. Effect of age on intraoperative cerebrovascular autoregulation and near-infrared spectroscopy-derived cerebral oxygenation. British Journal of Anaesthesia 2011; 107: 742–8.
21. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS- guided anaesthesia decreases postoperative delirium and cognitive decline. Journal of Neurosurgical Anesthesiology 2013; 25: 33–42.
22. Jildenstal PK, Hallen JL, Rawal N, Gupta A, Berggren L. Effect of auditory evoked potential-guided anaesthesia on consumption of anaesthetics and early postoperative cognitive dysfunction: a randomised controlled trial. European Journal of Anaesthesiology 2011; 28: 213–9.
23. Steinmetz J, Funder KS, Dahl BT, Rasmussen LS. Depth of anaesthesia and post-operative cognitive dysfunction. Acta Anaesthesiologica Scandinavica 2010; 54: 162–8.
24. Farag E, Chelune GJ, Schubert A, Mascha EJ. Is depth of anaesthesia, as assessed by the bispectral index, related to postoperative cognitive dysfunction and recovery? Anesthesia and Analgesia 2006; 103: 633–40.
25. White SM. Including the very elderly in clinical trials. Anaesthesia 2010; 65: 778–80.
26. Yun MJ, Oh AY, Kim KO, et al. Patient-controlled sedation vs. anaesthetic nurse-controlled sedation for cataract surgery in elderly patients. International Journal of Clinical Practice 2008; 62: 776–80.
27. Weaver CS, Hauter WH, Duncan CE, Brizendine EJ, Cordell WH. An assessment of the association of bispectral index with 2 clinical sedation scales for monitoring depth of procedural sedation. American Journal of Emergency Medicine 2007; 25: 918–24.

28. Young J, Inouye SK. Delirium in older people. British Medical Journal 2007; 33: 842–6.
29. Yang FM, Marcantonio ER, Inouye SK, et al. Phenomenological subtypes of delirium in older persons: patterns, prevalence, and prognosis. Psychosomatics 2009; 50: 248– 54.
30. Radtke FM, Franck M, Hagemann L, Seeling M, Wernecke KD, Spies CD. Risk factors for inadequate emergence after anes- thesia: emergence delirium and hypoactive emergence. Minerva Anestesiologica 2010; 76: 394–403.
31. Meagher D, Adamis D, Trzepacz P, et al. Features of subsyndromal and persistent delirium. British Journal of Psychiatry 2012; 200: 37–44.
32. Rudolph JL, Marcantonio ER. Postoperative delirium: acute change with long-term implications. Anesthesia and Analge- sia 2011; 112: 1202–11.
33. Ansaloni L, Catena F, Chattat R, et al. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. British Journal of Surgery 2010; 97: 273–80.
34. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. Journal of the American Medical Association 1996; 275: 852–7.
35. Tune L. Serum anticholinergic activity levels and delirium in the elderly. Seminars in Clinical Neuropsychiatry 2000; 110: 781–7.
36. Rudolph JL, Ramlawi B, Kuchel GA, et al. Chemokines are associated with delirium after cardiac surgery. Journal of Gerontology 2008; 63A: 184–9.
37. MacLullich AM, Edelshain BT, Hall RJ, et al. Cerebrospinal fluid interleukin-8 levels are higher in people with hip fracture with perioperative delirium than in controls. Journal of the American Geriatrics Society 2011; 59: 1151–3.
38. Ye X, Lian Q, Eckenhoff MF, Eckenhoff RG, Pan JZ. Differential general anesthetic effects on microglial cytokine expression. PLoS One 2013; 8: e52887.
39. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. Anesth Analg 2006;102(4):1267-73
40. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. Journal of the American Medical Association 1994; 271: 134–9.
41. Luetz A, Heymann A, Radtke FM, et al. Different assessment tools for intensive care unit delirium: which score to use? Critical Care Medicine 2010; 38: 409–18.
42. Radtke FM, Franck M, Schneider M, et al. Comparison of three scores to screen for delirium in the recovery room. Br J Anaesth 2008;101(3):338-43

43. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263-306.
44. José A. Aguirre, MD: Impact of RA on neurocognitive outcome / delirium
45. Rivera R, Antognini JF. Perioperative drug therapy in elderly patients. Anesthesiology 2009;110(5):1176-81.
46. Campbell N, Boustani MA, Ayub A, et al. Pharmacological management of delirium in hospitalized adults--a systematic evidence review. Journal of general internal medicine 2009;24(7):848-53|.
47. van den Boogaard M, Pickkers P, van der Hoeven H, Roodbol G, van Achterberg T, Schoonhoven L. Implementation of a delirium assessment tool in the ICU can influence haloperidol use. Crit Care 2009;13(4):R131.
48. Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340(9):669-76.
49. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373(9678):1874-82.
50. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age and ageing 2011; 40: 23-9.
51. Duggleby W, Lander J. Cognitive status and postoperative pain: older adults. Journal of pain and symptom management 1994;9(1):19-27.
52. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307(11):1151-60.
53. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301(5):489-99.
54. Cole MG. Delirium in elderly patients. The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry 2004;12(1):7-21
55. Rahkonen T, Luukkainen-Markkula R, Paanila S, Sivenius J, Sulkava R. Delirium episode as a sign of undetected dementia among community dwelling elderly subjects: a 2 year follow up study. J Neurol Neurosurg Psychiatry 2000;69(4):519-21
56. Pompei P, Foreman M, Rudberg MA, Inouye SK, Braund V, Cassel CK. Delirium in hos-

pitalized older persons: outcomes and predictors. Journal of the American Geriatrics Society 1994;42(8):809-15
57. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29
58. Hetherington R. The Snellen chart as a test of visual acuity. Psychologische Forschung 1954;24(4):349-57
59. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-98
60. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Annals of internal medicine 1993;119(6):474-81

61. Kalisvaart KJ, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. Journal of the American Geriatrics Society 2006;54(5):817-22.
62. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-Based Medicine. 2nd ed. Edinburgh, UK: Churchill Livingstone 2000
63. Evidence-Based Medicine Working G. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992;268(17):2420-5.
64. McAlister FA, Clark HD, van Walraven C, et al. The medical review article revisit-ed: has the science improved? Annals of internal medicine 1999;131(12):947-51
65. Mulrow CD. The medical review article: state of the science. Annals of internal medicine 1987;106(3):485-8.
66. Montori VM, Swiontkowski MF, Cook DJ. Methodologic issues in systematic re-views and meta-analyses. Clin Orthop Relat Res 2003(413):43-54.
67. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical ex-perts. Treatments for myocardial infarction. JAMA 1992;268(2):240-8.
68. Cook DJ, Sackett DL, Spitzer WO. Methodologic guidelines for systematic reviews of randomized control trials in health care from the Potsdam Consultation on Meta-Analysis. Journal of clinical epidemiology 1995;48(1):167-71.
69. Felson DT. Bias in meta-analytic research. Journal of clinical epidemiology 1992;45(8):885-92.

70. Wright RW, Brand RA, Dunn W, Spindler KP. How to write a systematic review. Clin Orthop Relat Res 2007;455:23-9|.
71. Mulrow C, Langhorne P, Grimshaw J. Integrating heterogeneous pieces of evidence in systematic reviews. Annals of internal medicine 1997;127(11):989-95.
72. Gotzsche PC. Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal antiinflammatory drugs in rheumatoid arthritis. Controlled clinical trials 1989;10(1):31-56.
73. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. Journal of the Royal Society of Medicine 2003;96(3):118-21.

74. Kranke P. Evidence-based practice: how to perform and use systematic reviews for clinical decision-making. Eur J Anaesthesiol 2010;27(9):763-72.
75. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explana-tion and elaboration. Journal of clinical epidemiology 2009;62(10):e1-34.
76. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). 2011.
77. American Psychiatric Association. Diagnostic and statistic manual of mental disorders, 4th edn. (text revision) (DSM-IVTR). Washington, DC, 2000.
78. World Health Organization. International Classification of Diseases (ICD). http://www.who.int/classifications/icd/en/ (accessed 28/10/2015).].
79. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj 2009;339:b2535.
80. Moyce Z, Rodseth RN, Biccard BM. The efficacy of peri-operative interventions to decrease postoperative delirium in non-cardiac surgery: a systematic review and meta-analysis. Anaesthesia 2014;69(3):259-69.
81. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. J Alzheimers Dis 2010;22 Suppl 3:67-79.
82. Kaneko et al 1999: Kaneko T, Cai J, Ishikura T, Kobayashi M, Naka T; Kaibara N. Prophylactic consecutive administration of haloperidol can reduce the occurrence of postoperative delirium in gastrointestinal surgery. Yonago Acta medica 1999;42:179–184.
83. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc. 2001;49(5):516-22.

84. Aizawa K, Kanai T, Saikawa Y, Takabayashi T, Kawano Y, Miyazawa N, Yamamoto T et al 2002: A Novel Approach to the Prevention of POD in the Elderly After GIT surgery. Surg Today. 2002;32(4):310-4.

85. Nishikawa K, Nakayama M, Omote K, Namiki A. Recovery characteristics and post-operative delirium after long-duration laparoscope-assisted surgery in elderly patients: propofol-based vs. sevoflurane-based anesthesia. Acta Anaesthesiol Scand. 2004; 48(2):162-8.

86. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, Eikelenboom P, van Gool WA. Haloperidol Prophylaxis for Elderly Hip-Surgery Patients at Risk for Delirium: A Randomized Placebo-Controlled Study. J Am Geriatr Soc. 2005;53(10):1658-66.

87. Liptzin B, Laki A, Garb JL, Fingeroth R, Krushell R. Donepezil in the Prevention and Treatment of Post-Surgical Delirium. Am J Geriatr Psychiatry. 2005;13(12):1100-6.

88. Papaioannou A, Fraidakis O, Michaloudis D, Balalis C, Askitopoulou H. The impact of the type of anaesthesia on cognitive status and delirium during the first postoperative days in elderly patients. Eur J Anaesthesiol. 2005;22(7):492-9.

89. Leung JM, Sands LP, Vaurio LE, Wang Y. Nitrous oxide does not change the incidence of postoperative delirium or cognitive decline in elderly surgical patients. Br J Anaesth. 2006;96(6):754-60.

90. Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB, Ames C, Chou D, Weinstein P.Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology. 2006;67(7):1251-3.

91. Taguchi T, Yano M, Kido Y. Influence of bright light therapy on postoperative patients: A pilot study. Intensive Crit Care Nurs. 2007;23(5):289-97.

92. Sampson EL, Raven PR, Ndhlovu PN, Vallance A, Garlick N, Watts J, Blanchard MR, Bruce A, Blizard R, Ritchie CW. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry. 2007;22(4):343-9.

93. Mouzopoulos G, Vasiliadis G, Lasanianos N, Nikolaras G, Morakis E, Kaminaris M. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. J Orthop Traumatol. 2009; 10(3): 127–133.

94. Larsen KA, Kelly SE, Stern TA, Bode RH Jr, Price LL, Hunter DJ, Gulczynski D, Bierbaum BE, Sweeney GA, Hoikala KA, Cotter JJ, Potter AW. Administration of Olanzapine to Prevent Postoperative Delirium in Elderly Joint-Replacement Patients: A Randomized, Controlled Trial. Psychosomatics. 2010;51(5):409-18.
95. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, Mears SC.Sedation Depth During Spinal Anesthesia and the Development of Postoperative Delirium in Elderly Patients Undergoing Hip Fracture Repair. Mayo Clin Proc. 2010; 85(1): 18–26.
96. Ono H, Taguchi T, Kido Y, Fujino Y, Doki Y. The usefulness of bright light therapy for patients after oesophagectomy. Intensive Crit Care Nurs. 2011;27(3):158-66.
97. Slor CJ, de Jonghe JF, Vreeswijk R, Groot E, Ploeg TV, van Gool WA, Eikelenboom P, Snoeck M, Schmand B, Kalisvaart KJ. Anesthesia and Postoperative Delirium in Older Adults Undergoing Hip Surgery. J Am Geriatr Soc. 2011;59(7):1313-9.
98. Marcantonio ER, Palihnich K, Appleton P, Davis RB. Pilot Randomized Trial of Donepezil Hydrochloride for Delirium After Hip Fracture. J Am Geriatr Soc. 2011;59 Suppl 2:S282-8.
99. Deschodt M, Braes T, Flamaing J, Detroyer E, Broos P, Haentjens P, Boonen S, Milisen K. Preventing Delirium in Older Adults with Recent Hip Fracture through Multidisciplinary Geriatric Consultation. Am Geriatr Soc. 2012;60(4):733-9.
100. Wang et al 2012: Haloperidol Prophylaxis Decreases Delirium Incidence in Elderly Patients after Noncardiac Surgery: a RCT.
101. Hempenius L, Slaets JP, van Asselt D, de Bock GH, Wiggers T, van Leeuwen BL. Outcomes of a Geriatric Liaison Intervention to Prevent the Development of Postoperative Delirium in Frail Elderly Cancer Patients: Report on a Multicentre, Randomized, Controlled Trial. PLoS One. 2013; 19;8(6):e64834.
102. De Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R, van Velde R, Levi M, de Haan RJ, de Rooij SE. Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. CMAJ. 2014;186(14):E547-56.
103. Fukata S, Kawabata Y, Fujisiro K, Katagawa Y, Kuroiwa K, Akiyama H, Terabe Y, Ando M, Kawamura T, Hattori H. Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial. Surg Today. 2014;44(12):2305-13.

104. Jia Y, Jin G, Guo S, Gu B, Jin Z, Gao X, Li Z. Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. Langenbecks Arch Surg. 2014;399(1):77-84.
105. Teslyar P et al 2013: Prophylaxis with antipsychotic medication reduces the risk of postoperative delirium in elderly patients: a meta-analysis. Psychosomatics. 2013;54(2):124-31.

9. Curriculum Vitae

Name, Vorname	Pellegrino, Alejandro
Geschlecht:	männlich
Geburtsdatum:	10.09.1992
Heimatort und Kanton	Zürich, ZH

Ausbildung:

2010-2017	Medizinstudium an der Universität Zürich
2004-2010	Wirtschaftsprofil mit zweisprachiger Matur (Gymnasium), Kantonsschule Enge
2002-2004	Primarschule in Horgen (ZH)
1998-2002	Primarschule in Locarno (TI)

Erklärung

Masterarbeit

Ich erkläre ausdrücklich, dass es sich bei der von mir im Rahmen des Studiengangs

Humanmedizin M Med eingereichten schriftlichen Arbeit mit dem Titel

The effects of perioperative interventions on postoperative delirium in non-cardiac surgery: A systematic review

um eine von mir selbst und ohne unerlaubte Beihilfe sowie *in eigenen Worten* verfasste Masterarbeit* handelt.

Ich bestätige überdies, dass die Arbeit als Ganzes oder in Teilen weder bereits einmal zur Abgeltung anderer Studienleistungen an der Universität Zürich oder an einer anderen Universität oder Ausbildungseinrichtung eingereicht worden ist.

Verwendung von Quellen

Ich erkläre ausdrücklich, dass ich *sämtliche* in der oben genannten Arbeit enthaltenen Bezüge auf fremde Quellen (einschliesslich Tabellen, Grafiken u. Ä.) als solche kenntlich gemacht habe. Insbesondere bestätige ich, dass ich *ausnahmslos* und nach bestem Wissen sowohl bei wörtlich übernommenen Aussagen (Zitaten) als auch bei in eigenen Worten wiedergegebenen Aussagen anderer Autorinnen oder Autoren (Paraphrasen) die Urheberschaft angegeben habe.

Sanktionen

Ich nehme zur Kenntnis, dass Arbeiten, welche die Grundsätze der Selbstständigkeitserklärung verletzen – insbesondere solche, die Zitate oder Paraphrasen ohne Herkunftsangaben enthalten –, als Plagiat betrachtet werden und die entsprechenden rechtlichen und disziplinarischen Konsequenzen nach sich ziehen können (gemäss §§ 7ff der Disziplinarordnung der Universität Zürich sowie §§ 51ff der Rahmenverordnung für das Studium in den Bachelor- und Master-Studiengängen an der Medizinischen Fakultät der Universität Zürich

Ich bestätige mit meiner Unterschrift die Richtigkeit dieser Angaben.

Datum: 14.01.2017

Name: Pellegrino Vorname: Alejandro

Unterschrift:……..*nur auf Printversion erforderlich*

* Falls die Masterarbeit eine Publikation enthält, bei der ich Erst- oder Koautor/-in bin, wird meine eigene Arbeitsleistung im Begleittext detailliert und strukturiert beschrieben.